Human Exposure Assessment for DEET

By

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EXECUTIVE SUMMARY

DEET Human Exposure Assessment

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Purpose

The Department of Pesticide Regulation (DPR) prepared an exposure assessment for DEET (*meta*-methyl *N,N*-diethyl toluamide) because of observations of adverse neurological outcomes in laboratory animal studies and reports from the published literature of neurological symptoms in children treated with this repellent for protection from nuisance or disease-transmitting arthropods. Comparison of the exposure data with the information derived from animal toxicology studies allows the estimation of risk and/or oncogenic potential during use of products containing DEET.

BACKGROUND

Humans apply DEET to their skin and clothing to repel nuisance and disease-transmitting arthropods. Extensive data exist on the use patterns of DEET, human absorption, and metabolism after skin application. In the time period between 1982-1995, 11 illnesses or injuries were reported to DPR for products containing this active ingredient.

METHODS

The document summarizes the exposure information on DEET from the peer-reviewed published literature and from companies that sell products containing this active ingredient. The data utilized for the development of the exposure assessment included a national survey of use characteristics of DEET (formulation type, time of year, amount used for each application), and human pharmacokinetics and metabolism after dermal treatment. From this information, we derived estimates of daily, annual and lifetime exposure.

FINDINGS AND CONCLUSIONS

For a single application of DEET, daily absorbed dosages were 1076 and 1661 μg/kg in adult females and children 12 years or younger, respectively. The Annual Average Daily Dosage (AADD) for DEET ranged from ~37-130 μg/kg/day for the different age groups. When the exposure information is compared to the animal toxicology data, DPR can estimate risks associated with the use of this arthropod repellent.

VOLUME 2

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
WORKER HEALTH AND SAFETY BRANCH

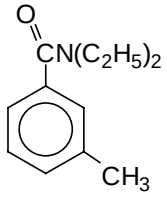
HUMAN EXPOSURE ASSESSMENT

DEET

January 20,1999

INTRODUCTION

DEET, *N,N* diethyl *meta*-toluamide, (CAS No. 134-62-3, formula $C_{12}H_{17}NO$, MW 191.27) is a repellent applied to humans for protection from biting arthropods, primarily mosquitoes, fleas and ticks. Some of these species are vectors for diseases, such as, Rocky Mountain Spotted Fever, Lyme's Disease, malaria, encephalitis and human granulocytic ehrlichiosis. The structure of DEET is shown below:



Some physical-chemical properties of DEET are listed below [a/]:

Boiling Point (°C,1.3 mbar)	111
Vapor Pressure (Pa, 25 °C)	0.22
K_{ow}	2.0

[a/] Tomlin, 1994

EPA STATUS

The US Environmental Protection Agency (US EPA) has DEET under review because of concerns about adverse health effects after use. As a part of this process, they are considering additional label language to reduce the frequency of illness associated with use of this repellent.

USAGE

Since DEET is not applied in production agriculture, its use is not required to be reported in California under the full Pesticide Use Report process. However, California sales data are available and provide some indication of use in California. Table 1 contains a compilation of the pounds of DEET products and DEET sold in 1991-1995.

Table 1. Pounds of DEET Products and DEET Sold in California: 1991-1995[a/]

	Pounds Sold	
Year	DEET Products	DEET
1991	588,101	119,389
1992	708,797	145,735
1993	1,771,522	363,354
1994	810,780	129,478
1995	590,472	104,082
Mean	895,534	172,408
SD	445,459	96,430

Mill Tax Assessment Database[a/]

Sanborn, WHS, 1999

These data demonstrate approximately a three-fold variability in the amount of product sold from year to year. Using the ratio of pounds sold for DEET and DEET products, the average percent of active ingredient in DEET products is 19.3% (range 16-20%) for the 5 years evaluated. This value is similar to the estimate of ~24.5% percent active ingredient that was based on a national survey (see Table 10).

FORMULATIONS

Accessible via the department web site, the Department of Pesticide Regulation (DPR) label database lists 164 currently registered products that contain DEET as the active ingredient. DEET is formulated as an aerosol, gel, cream, spray and ready-to-use liquid, to name a few.

LABEL PRECAUTIONS

The following label precautions are listed on a product containing 100% DEET. The product has the signal word **CAUTION.** This was selected as an example of a label because it provides the maximum likelihood for potential effects that may result from exposure to this repellent.

DO NOT APPLY TO EYES AND MOUTH. MAY CAUSE EYE INJURY. DO NOT SPRAY DIRECTLY ON FACE. DO NOT APPLY TO HANDS OF YOUNG CHILDREN. DO NOT APPLY TO SEVERELY SUNBURNED OR OTHERWISE DAMAGED SKIN.

ILLNESSES

The Pesticide Illness Surveillance Program data indicates that there were 11 reports of illness related to DEET exposure from 1982 through 1995 (WH&S, 1999). The types of illness reported were systemic (2), eye (6) and skin (3). Two days of lost work time were reported for 9 of the 11 cases; in two reports, lost work time is unknown. No days of hospitalization are reported for any of the exposures. Only one non-occupational incident was reported; an individual experienced and allergic reaction after spraying an entire can of DEET in his van. There were 10 occupational incidents: three persons sprayed DEET directly onto their eyes; two were exposed when handling defective containers; and two suffered possible allergic reactions; and three had DEET transfer from skin to eyes or mouth via sweat or rubbing.

TOXICITY

Acute toxicity by the dermal route is likely to be low, since the acute oral toxicity (LD_{50}) for male rats is reported as ~2,000 mg/kg (Tomlin, 1994). The acute dermal LD_{50} values in the rat, mouse and rabbit, are 5000 mg/kg, 3170 µl/kg and 3180 µl/kg, respectively (RTECS, 1997). The latter two values are reported in unconventional units of volume. Since the density of DEET is 0.996 g/l, these microliter values are numerically equivalent to milligrams.

DERMAL ABSORPTION

The dermal absorption of DEET has been investigated in rats, hairless dogs, monkeys and humans. The following discussion summarizes these studies.

Rats (single application)
Male Sprague-Dawley rats (6-8) were dosed (44 µg/4.2 cm^2 in 100 µl acetone) mid-dorsally with ^{14}C-ring-labeled DEET (specific activity 4.35 mCi/mmole, >98% pure), Moody *et al.*, 1989. The treated area was washed at 24 h with 50% Radiac® soap. The amount absorbed in 24 h was determined to be 36 ± 8% by analysis of the excreta. The urinary $t_{1/2}$ after dermal application was observed to be 20 h.

Monkeys (single application)
Rhesus monkeys (6-8) were dosed similarly to the rat, except several anatomical sites were treated to determine the effect on absorption (Moody *et al.*, 1989). The dermal absorption values after application to various sites are shown in Table 2. These ranged from 14% for the middorsal forearm to 68% for the ventral forepaw. The elimination

half-life followed the magnitude of dermal absorption with 4 h for the middorsal forearm to 8 h for the ventral forepaw.

Table 2. Influence of Anatomical Site on the Dermal Absorption of ^{14}C-DEET in Monkeys

Anatomical Site	Absorption (%)	Urinary $T_{1/2}$ (h)
Middorsal Forearm	14 ± 50	4
Forehead	33 ± 11	6
Dorsal Forepaw	27 ± 30	7
Ventral Forepaw	68 ± 90	8

Moody *et al*., 1989

Rat/Monkey (multiple applications)

In addition to the single administration studies, Moody *et al.* (1989) evaluated multiple dermal applications of DEET made to the forearm of monkeys and the dorsum of rats (Table 3). These experiments were conducted to determine whether there was a difference in dermal absorption between multiple and single applications. This is particularly relevant for humans as this repellent is generally applied several times daily to provide continued protection against biting arthropods. Multiple skin applications are required for continued efficacy because loss occurs from volatilization and dermal absorption.

Table 3. Influence of Multiple Applications of DEET on Dermal Absorption and Urinary Half-Life ($t_{1/2}$) in Rats and Monkeys

Animal	No. Applications	Time Interval (hr)	Absorption (%)	Urinary $t_{1/2}$ (h)
Rat	1	-	36 ± 8	20
Rat	3	2	31 ± 5	16
Monkey	1	-	14 ± 5	4
Monkey	3	0.5	12 ± 1	4

Moody *et al*., 1989

These data indicate that multiple applications of DEET do not markedly affect either the magnitude of the absorbed dose or the urinary half-life. With respect to the time interval between applications, the study in rats appears to be most relevant to human use of this repellent. It is improbable that a human would apply DEET three times in 0.5 h, as attained in the monkey study. While humans may apply DEET twice during a 2-hour period, this is still likely an excessive use, even in an area where the biting arthropod pressure is very high. It is more likely that humans may apply this repellent several times in a 16-hour period, with 2-4 h elapsing between applications. Despite improbability of humans using DEET twice during a 2-hour period, these data clearly demonstrate that multiple DEET dermal applications over relatively short time frames do not significantly impact the dermal absorption or the elimination half-life of this repellent.

Hairless Dog (single application)

Reifenrath *et al*., 1981 investigated dermal absorption of undiluted DEET in the hairless dog. Two dose rates were used, 340 and 4 µg/cm^2. Three dogs were used per dose with a study duration of 96 h. Using an intravenous (iv) dose, the dermal absorption estimate was corrected for incomplete urinary excretion. Dermal absorption values for the high and low doses were 9.4 ± 3.6% and 12.8 ± 4.6%, respectively. Considering variability, the latter value is comparable to that obtained by Feldmann and Maibach, 1970, where humans were treated at the same dose rate. The high treatment rate is also similar to the values employed in the human studies by Selim, 1991a, 1991b, and 1992, and Selim *et al.,* 1995, where the doses were about 1.5-fold higher than this dog study.

Humans

Feldmann and Maibach, 1970, investigated the dermal absorption of DEET in humans. Subject's forearms (4) were treated with ^{14}C-labeled DEET in acetone (position of label, specific activity and radiopurity unspecified) at a dose of 4 µg/cm^2. The site of application was not covered or washed for 24 h. Urine samples were collected 120 h post-application for analysis of radioactivity. Since the study did not indicate the amount of radioactivity removed by washing at twenty-four hours, it is not possible to determine the material balance. Data from an iv administration of DEET were used to estimate incomplete renal excretion after dermal absorption. The iv administration data indicated that 52.3% radioactivity was recovered in the urine with a $t_{1/2}$ of 4 h. For dermally administered DEET, 16.7% (SD = 5.1%) was absorbed over the duration the study. By contemporary criteria this study has some deficiencies (estimate of material balance, metabolite characterization, solvent relevance to a commercial formulation). However, when the ~17% dermal absorption is compared with later investigations in other animals, including non-human primates (Moody *et al*., 1989), this value compares favorably.

The loss of DEET's repellent efficacy over time results from skin absorption/adsorption and volatilization from the site of application (Moody *et al*., 1989, Spencer *et al.*, 1979). Evaporative loss is important for repellency of biting arthropods. Spencer *et al*., 1979 investigated, in some detail, the loss of DEET from both *in vitro* and *in vivo* skin and found 30-45 min. post application, the evaporation rate was 4.0 ± 2.9 and 3.5 ± 1.6 µg/cm^2/h, respectively. These data can be used to estimate material balance for the Moody *et al. in vivo* studies: 9.6% evaporated; 27.1% associated with a skin wipe; and 11.9% associated with skin stripping for a total recovery of 48.3%. The dose rate of 25 µg/cm^2 in these *in vitro* experiments by Spencer *et al.,* 1979 lies in the range (10-70 µg/cm^2) that is effective for the repellency of biting arthropods (Gabel *et al*., 1976).

In the multiple dermal absorption studies reported by Moody *et al.*, 1989, one male subject was treated on the back, chest, and forearm with 15g of a commercial insect repellent formulation containing 95% DEET (Muskol®, dose rate = 3,450 µg/cm²) or 14.25 g DEET (dose rate = 3,277.5 µg/cm²). This dose rate is 47-325 fold greater than those found to be effective for arthropod repellency (Gabel *et al*., 1976). The male human subject showered four hours after treatment. Urine samples were collected for

48 h post administration. Table 4 contains the data for the time dependent elimination of DEET and the primary metabolite, *N*-ethyl *m*-toluamide (NEMT).

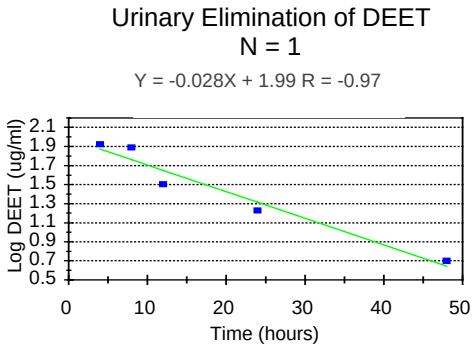
Table 4: Urinary titers of DEET and NEMT after treatment of a single human male with 15g Muskol®

Time (hrs)	DEET (µg/ml)	NEMT (µg/ml)
0	9 ± 8	4 ±< 1
4	84 ± 62	11 ± 97
8	78 ± 38	129 ± 11
12	32 ± 28	28 ± <1
24	17 ± <1	20 ± 1
48	5 ± <1	35 ± 16

Moody *et al*., 1989

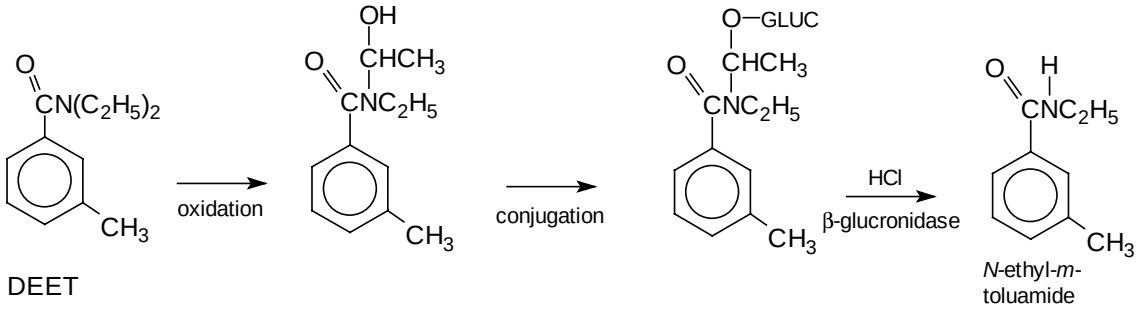
The units (µg/ml) do not allow estimation of a cumulative excreted dose because the urine volumes at each time period were not provided. Therefore, it is not possible to estimate either the total amount of DEET or NEMT at each sampling period. Further, it is not possible to estimate the percent absorbed in this study. However, it is possible to estimate a urinary half-life for elimination of DEET, but not for the metabolite, NEMT. A value for the half-life for NEMT cannot be estimated because the urinary metabolites reach a plateau at 48 h with no apparent decrease in their titer during the duration of the study. The half-life for elimination of DEET from this single subject was 10.7 h. This is less than the value for rats (16-20 h) and greater than the values for the monkey (4-8 h). The plot of these urinary data is shown below

Figure 1



In the study by Moody *et al*., 1989 NEMT (Figure 2) was isolated after treatment of the urine samples with acid or β-glucuronidase. The structure was determined by gas chromatography coupled with mass spectrometry (GC/MS). Since this metabolite does not contain a hydroxyl or amine moiety, it is not obvious why treatment was required to isolate this metabolite. An explanation for the need for either treatment is that the intermediate from oxidative metabolism was immediately conjugated as a glucuronide. Support for excretion of a metabolite of DEET as a glucuronide may be found in the earlier work of Wu *et al*., 1979.

Figure 2



Wu *et al.*, 1979, focused on spectroscopic identification of the various metabolites in urine present after dosing. An individual treated himself topically with 10.5 g of a 75% formulation (7.88 g DEET). Small amounts of the intermediate hydroxylated species following acid hydrolysis were observed spectroscopically; it resulted in formation of NEMT. This is only an inference for the presence of the glucuronide in urine, as the authors did not isolate the glucuronide for mass spectral analysis. Interestingly, the authors found small amounts of methyl-oxidized products, namely the alcohol and carboxylic acid. The latter was transformed into the methyl ester for characterization. In addition, Wu *et al.,* 1979, found unmetabolized DEET in the urine. This constituted 10-14% of the applied dose (133 mg/kg) in the first hour and ~2% at the fourth hour. In blood, at 8 h the concentration of DEET was determined to be 0.3% (300 µg/100 ml blood). At 18 h after application detectable DEET was still in the urine. At the end of the study, the carboxylic acid, before methylation was determined to be the major human metabolite in the urine. In the most recent human dermal absorption study (to be discussed later in this document) the carboxylic acid metabolite was observed via use of high-pressure liquid chromatography (HPLC) (Selim, 1992 and Selim *et al*., 1995).

Recently, the DEET Steering Committee, evaluated the dermal absorption in humans (Selim, and 1992 and Selim *et al*., 1995). The forearms of twelve healthy volunteers (six/formulation) were treated with 12-15 mg ^{14}C-ring-labeled DEET (98.9% radiopurity, 97.87% chemical purity, specific activity 22 mCi/mmole) either undiluted or as a 15% (w/v) solution in ethanol. The dosing area was 24 cm^2 (6X4 cm). Those treated with the 15% material received a dose of ~500 µg/cm^2. For subjects administered undiluted DEET, the dose was slightly higher, 620 µg/cm^2. The treated area was covered with an aluminum dome that contained air holes for circulation, but prevented physical contact with the ^{14}C-DEET. At 8 h post-treatment, the cover was removed and the treated area washed with *iso*-propanol moistened cotton swabs. Tape strippings of the treated area were conducted at 1, 23 and 45 h after the cover and protective wrappings were removed. Blood samples from the treated and untreated arms were taken at 0, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 h post application. Urine samples were collected at 0-4, 4-8, 8-12, 12 to 120 h and then 120-128 h. The subjects were not allowed to bathe until the last tape stripping was completed 45 h after the protective

appliance was removed. At the end of the eight-hour exposure period, the location of administered doses for the two treatments were marked on the skin.

Table 5: Distribution of ^{14}C-DEET equivalents after application to human volunteers: Effect of formulation

	Percent of Applied Dose	
Region	Undiluted	15% in Ethanol
Swabs	60.80	50.89
Pipettes	5.33	2.46
Skin rinse	1.14	1.05
Gauze	0.28	0.32
Aluminum dome	21.08	25.54
Tape Stripping	0.08	0.07
Feces	0.02	0.08
Urine	5.61	8.33
Total	94.34	88.74

Sanborn, WH&S, 1999 after Selim, 1992 and Selim *et al*., 1995

While this study did not utilize an iv dose to correct for incomplete renal elimination, sufficient data exists for a material balance calculation and estimation of dermal absorption.

The following table compares the dermal absorption values from Feldmann and Maibach, 1970 and Selim, 1992 and Selim *et al*., 1995.

Table 6: Comparison of Dermal Absorption of DEET in Humans

Study	Vehicle	Dose Rate (μg/cm^2)	Absorption (%)
Feldmann & Maibach	Acetone	4	16.7 (5.1)[a/]
Selim	None	620	5.6 (2.8)
Selim	Ethanol	500	8.4 (3.6)

a/ Arithmetic standard deviation

Sanborn, WH&S, 1999

Despite the 125-fold greater dose rates (500 and 600 μg/cm^2) in the studies by Selim, 1992, and Selim *et al*., 1995 vs. those by Feldmann and Maibach, 1970, (4 μg/cm^2) only a two-fold difference exists in the dermal absorption when a solvent was utilized (16.7% vs. 8.4%). In the studies by Selim, 1992 and Selim *et al*., 1995 where the dose rates were comparable (620 vs. 500 μg/cm^2), the difference in dermal absorption is likely related to use of the ethanol as a dosing vehicle. Considering the variability in the Selim data (cv ~43%), the dermal penetration values for the studies with solvent are likely the same. Statistical treatment of these data with a 2-tailed t-test for independent samples indicates that they are not different at $p \leq 0.05$ and are only different at $p = 0.24$. This assumes equal variances. The Selim study used dose rates about 10-fold higher than are reported by Gabel *et al.*, 1976 to provide protection from nuisance

arthropods (10-70 ug/cm^2). These higher dose rates may be related to the specific activity of the radiolabeled DEET.

METABOLISM

Humans

In contrast to the report by Moody *et al*., 1989, following dermal administration, Selim, 1992 and Selim *et al*., 1995 found two urinary metabolites of DEET; these are depicted below:

Figure 3

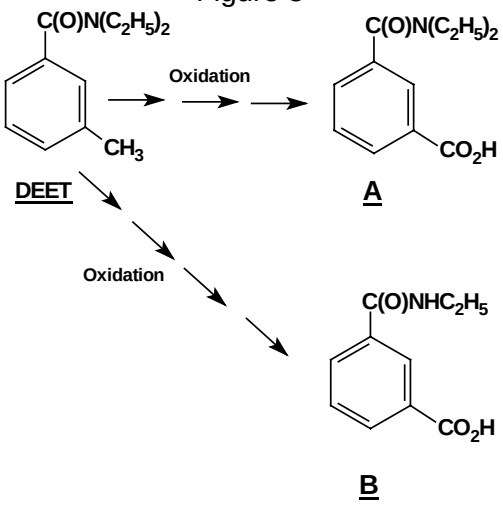


Table 7 presents the mean percentages of these two metabolites in the urine, as well as, the percentage of these metabolites as a function of the applied dose.

Table 7: Urinary Metabolites in Humans after Dermal Dosing of DEET in Two Formulations

DEET Dosing Regime	Metabolite	% Metabolite in Urine	% Metabolite Applied Dose
15% in Ethanol	A	32.6	2.7
15% in Ethanol	B	16.0[a/]	1.1
Undiluted	A	34.6	2.0
Undiluted	B	11.0[a/]	0.7

[a/] Likely underestimated because of incomplete resolution on HPLC

Sanborn, WH&S, 1997 after Selim, 1992 and Selim *et al*., 1995

These metabolites were not identified spectroscopically (mass spectrometry), but were characterized qualitatively by comparison of relative retention times on HPLC to those initially observed in a rat metabolism study after an oral dose. The difficulty of resolving metabolite B from another urinary metabolite interferes with precise quantitation of this degradation product. The small fraction of the applied dose as identifiable metabolites

may make exposure assessment from urinary biomonitoring of humans exposed to DEET somewhat difficult unless small inter- and intra-individual variation exists for these metabolites. If small variation is observed, then it might be possible to use these metabolites as biomarkers of DEET exposure.

Comparison of these metabolism data with data from Moody *et al.*, 1989, provides a different picture of the human metabolites. None of the degradation products in Selim's work were found in Moody's study and vice versa. The apparently facile benzylic oxidation of the methyl moiety in DEET observed in the investigations by Selim is not unexpected.

EXPOSURE ASSESSMENT

Non-occupational

Using several types of surveys, researchers estimated exposure of humans to DEET in non-occupational settings (Boomsma and Parthasarathy, 1990). These surveys consisted of a mail survey, usage survey and a syndicated market share survey. In the syndicated market survey, data was gathered on products sold, timing of sales, etc.

The mail survey was sent to 8,000 households, nationally balanced to the US Census data on age, household income, region, population and household size. Questionnaires asked people about insect repellent use in the last year. If anyone in the household responded positively, the household was targeted for further study and asked to keep a daily diary of repellent use during June and July. In the diary, information was recorded on date of use, who used it, brand name and number of applications. June and July were selected because sales data show most repellents are sold in these months; this time period accounted for 53-60% of annual use.

In the usage survey, 542 individuals were observed applying DEET products. Observers recorded areas treated, whether applied to clothes, skin or both, whether label directions were followed and the amount applied (product weighed before and after use). The use survey was conducted in Green Bay, Wisconsin, Tampa, Florida and Portland, Oregon, representing high, medium and low exposure, respectively. Even though this was not California-specific data, the information from this national survey will be used to estimate exposure of Californians to DEET.

Type of Products. Table 8 lists DEET products sold in 1989 and 1990 and the results of the 1990 use survey for these same products. Data from the market survey and use survey show good concordance.

Frequency of Use. Table 9 contains data on insect repellent use from the initial mail survey. Obviously, households targeted for further study reported higher use of DEET; about 4 out of 5 respondents indicated that they had used an insect repellent sometime in the previous year. For the whole survey population, about 3 out of 10 reported use of an insect repellent during the previous year. Neither of these surveys total 100% because of non-respondents.

Table 8: Market Share of DEET Products Sold in 1989 and 1990 and 1990 Usage Study

Formulation Type	Market Share (%)[a/] 1989	1990	Use Survey (%)[b/]
Aerosol	75.5	71.9	75
Pump Sprays	15.6	15.0	16
Lotions/Creams	1.3	1.4	6
Liquids	4.8	6.0	1
Roll On/Stick	0.8	0.7	1
Towellettes	2.0	0.2	1
Other	-	4.8	-

[a/] Table 6, Boomsma and Parthasarathy, 1990
[a/] Table 41, Boomsma and Parthasarathy, 1990

Boomsma and Parthasarathy, 1990

Table 9: Frequency of DEET Use in Mail Survey; Use of Any Insect Repellent in Previous Year

Household	Sample Size	Yes (%)	No (%)
Initial Survey Population[a/]	12,224	37	62
Targeted Survey Population[b/] (later kept diary of use)	5,536	82	17

[a/] Table 7, Boomsma and Parthasarathy, 1990
[b/] Table 8, Boomsma and Parthasarathy, 1990

Boomsma and Parthasarathy, 1990

Data from the mail survey indicated that during June and July of 1990, people used DEET products an average of 7.5 times (N=1,571).

Usage Amounts. Table 10 shows the distribution of the amount of DEET product and amount of DEET applied during a one-time application to skin and clothing. As stated before, these data were obtained by weighing the product container before and after use, ensuring an accurate determination of the amount of DEET used.

Table 10: Amount of DEET Product and DEET Applied to Skin and Clothing from a single application

DEET Product[a/]		DEET[b/]	
Amount of Product Applied (g)	Percent of Population	Amount of DEET Applied(g)	Percent of Population
0.0-2.99	40	0.00-0.99	56
3.0-5.99	32	1.00-1.99	27
6.00-8.99	15	2.00-2.99	10
9.00-11.99	5	3.00-3.99	5
12.00-14.99	5	4.00-4.99	1
≥15.00	3	5.00-5.99	1
		≥6.00	1
Mean (g) = 4.9[c/]		Mean (g) = 1.2[c/]	

[a/] Table 46, Boomsma and Parthasarathy, 1990; Sample size = 542
[b/] Table 51, Boomsma and Parthasarathy, 1990; Sample size = 542
[c/] Mean: midpoint applied range x percent population use, summed/100; therefore it is a weighted mean

After Boomsma and Parthasarathy, 1990

The mean amount used allows estimation of the approximate percent DEET in the products applied for arthropod repellency. These data indicate that DEET products used contain an average of 24.5% DEET (1.2/4.9 X100).

Estimation of Daily Potential Exposure and Absorbed Daily Dosage (ADD). The following exposure and dosage estimates use data from application to skin only. Table 11 provides information on the variability of the DEET exposure data. The exposure values in this table represent the overall mean for the population, including all formulations, age groups and both sexes, mean + 2 standard deviations (SD) and the 90^{th} and 95^{th} percentiles. (No justification was provided in the reference exposure document for the calculation of the upper end values.) The small variability in these data is somewhat unexpected. In contrast, exposure studies conducted in production agriculture generally exhibit large ranges, often more than 10-fold. Production agriculture exposure data are therefore often log-normally distributed, requiring geometric statistical treatment to calculate central tendencies. In contrast, for these aggregate population data, the difference between the mean value and the 95th percentile is less than 4-fold. Apparently the self-application of DEET or application to others does not have the variability routinely observed in other exposure studies.

Table 11: DEET Exposure to the Skin - Data Variability (All age groups)

	Aggregate Mean Exposure[a/]			
Exposure	(g/day)	g/day + 2 SD[b/]	g/day (90^{th})[c/]	g/day (95^{th})[d/]
Skin Only	0.038	0.042	0.081	0.12

[a/] From Table 4, Boomsma and Parthasarathy; Total overall average (composite all age groups)
[b/] SD-Standard Deviation
[c/] 90^{th} percentile
[d/] 95^{th} percentile

Sanborn, WH&S, 1999, after Boomsma and Parthasarathy, 1990

To understand the data in Tables 12 and 13, annual average daily dosages (AADD) and seasonal average daily dosages (SADD values), it is necessary to provide some information on how the data in these tables were derived. From the usage survey, researchers determined the amount applied per application. From the mail survey, users reported the number of applications during the heavy-use months (June and July). To obtain the total amount used during the heavy use months, the amount per application was multiplied by the number of applications. To derive the average yearly and daily amount used the following two equations were used:

$$\text{Average Yearly DEET Use (g)} = \frac{\text{Average DEET usage in June/July}^{1/}}{\text{\% Yearly Product Sold in June/July}}$$

[1/] Grams/application x # application

$$\text{Average Daily DEET Use (g)} = \frac{\text{Average Yearly DEET Use}}{365 \text{ days}}$$

Data in Table 11 reflect an overall mean for the general population (male, female, and all age groups). In addition, it may be important to derive values for different age groups (Table 12). While the amount of DEET applied in each age group is relatively constant (less than two-fold difference), the body weights of the different ages differ more than 10-fold from infants/children to adults. Mean weights were selected from the US EPA Exposure Factors Handbook (US EPA, 1996). When there is a range of ages, *i.e.*, for young children <12, the weight at the midpoint of the age (*i.e.* 1-12 y) is utilized. The exposure data in the table below only indicates about a 3.6-fold variation. Table 12 summarizes these age-related exposures.

Table 12: DEET Exposure by Age and Gender - Annual Average Daily Dosage (Skin Only)

Gender:	Male	Female	Male	Female	Male	Female
Age Group:	Adult	Adult	(13-17)	(13-17)	(<12)	(<12)
Dermal Exposure (g/d)[a/]	0.053	0.029	0.037	0.037	0.034	0.034
Body Wt (kg)	78.1	65.4	61.1[c/]	55[c/]	22.8[c/]	21.9[c/]
AADD (µg/kg/d)[b/]	57.0	37.1	50.7	56.4	124.5	129.6

[a/] From Table 4, Boomsma and Parthasarathy, 1990, Annual Averaged Daily Dermal Exposure
[b/] Annual Average Daily Dosage: Dermal absorption = 8.4% (Selim, 1992); sample calculation for male 0.053 g/day/78.1 x 0.084 x 10^6 µg/g = 57 µg/kg/day
[c/] Body weight-midpoint of the age range, Draft US EPA Exposure Factors Handbook, 1996

Sanborn, WH&S, 1999 after Boomsma and Parthasarathy, 1990

If there are age-related concerns regarding the use of DEET as a repellent, then these exposure data can be used with the toxicology information to provide either estimates of risk or margins of exposure (MOE). The greater AADD values of children less than 12 yr. as compared to adults are the result of lower body weight and data from the usage survey where approximately the same amount was applied to this age group despite the smaller surface area.

An aspect of the exposure estimates in Table 12 is unreasonable from a use perspective. The adult female daily dermal exposure is less than either of the younger age groups. In terms of body weight, the adult female is not much different than the 13-17 year old male as indicated in Table 12. A modified exposure assessment will be derived later in the document that takes into account both surface area and body weight of the different age groups.

Seasonal Average Daily Dosage

Data from a single exposure can be amortized over time to obtain a Seasonal Average Daily Dosage. From the mail survey, we know people used DEET an average of 7.5 times per season. Table 13 contains the seasonal dosage by gender and age.

Table 13: Seasonal Average Daily Dosage (SADD) by Age from 7.5 Applications (Skin Only)

Gender:	Male	Female	Male	Female	Male	Female
Age Group:	Adult	Adult	(13-17)	(13-17)	(<12)	(<12)
Exposure (g/d)[a/]	0.95	0.65	1.07	1.07	0.94	0.94
Body Wt (kg)	78.1	65.4	61.1[c/]	55[c/]	22.8[c/]	21.9[c/]
SADD (μg/kg/d)[b/]	125.6	102.6	180.9	200.9	425.8	443.3

[a/] From Table 50, Boomsma and Parthasarathy, 1990
[b/] Seasonal Average Daily Dosage: Dermal absorption = 8.4% (Selim, 1992; Selim *et al*., 1995), Sample calculation for male: (0.95 g/day x 7.5 applications/season / 61 days/season) / 78.1 kg x 0.084 x 10^6 μg/g = 125.6 μg/kg/day
[c/] Body weight-midpoint of the age range, Exposure Factors Handbook, US EPA, 1996

Sanborn, WH&S, 1999 after Boomsma and Parthasarathy, 1990

Absorbed Daily Dosages from a Single Application. The estimates of ADD values from a single application are compiled in Table 14.

Table 14: Exposure by Age from a Single Application (Skin Only)

Gender:	Male	Female	Male	Female	Male	Female
Age Group:	Adult	Adult	(13-17)	(13-17)	(<12)	(<12)
Exposure (g/d) [a/]	0.95	0.65	1.07	1.07	0.94	0.94
Body Wt (kg)	78.1	65.4	61.1[c/]	55[c/]	22.8[c/]	21.9[c/]
ADD (μg/kg/d)[b/]	1,020	840	1,470	1,630	3,460	3,610

[a/] From Table 50, Boomsma and Parthasarathy, 1990
[b/] Absorbed Daily Dosage: Dermal absorption = 8.4% (Selim, 1992; Selim *et al*., 1995), Sample calculation for male: 0.95 g/day/ 78.1 kg x 0.084 x 10^6 μg/g = 1,020 μg/kg/day
[c/] Body weight-midpoint of the age range, Exposure Factors Handbook, US EPA, 1996

Sanborn, WH&S, 1999 after Boomsma and Parthasarathy, 1990

Comparison of the SADD data in Table 13 with AADD values in Table 12 indicates that seasonal exposure is significantly greater. This not unexpected given the reduction in exposure that occurs when exposure is amortized over a use season or over an entire year.

Alternative Non Occupational Exposure Assessment

As indicated earlier, the exposure estimates in Tables 12-14 are not logical, even though they are based on a usage survey of considerable size. It is unrealistic to think that a child less than 12 years old will receive approximately the same dermal dose as older age groups when the surface area is considerably less. Table 15 contains an alternative dermal exposure assessment for users of products containing DEET. Two assumptions were used to develop the data in this table: 1) the adult male applies 1,000 mg each application and 2) the treated area for the male is 1.94 m^2.

The surface area (1.94 m^2) is the 50 percentile in the US EPA Exposure Factors Handbook (US EPA, 1996). The dermal doses for the other age groups were derived from the adult male dose in mg/cm^2 and the body surface area of each age group. To obtain the ADD values a dermal penetration value of 8.4% and the appropriate body weights were utilized.

Table 15. DEET Dermal exposure and absorbed daily dosage (ADD): Single application Basis: Surface Area and Body Weight for Three Age Groups

	Adult Male	Adult Female	Child 12-17	Child < 12
SA (m^2)[a/] 50 percentile	1.94	1.69	1.58[b/]	0.86[b/]
Dermal Dose (mg/per/applic.)	1000	871[c/]	814[c/]	443[c/]
BW (kg)	78.1	65.4	58.1[d/]	22.4[d/]
Dermal Dose[e/] (mg/kg)	12.8[e/]	13.3	14.0	19.8
ADD[f/] (µg/kg/d)	1076	1119	1177	1661

[a/] Exposure Factors Handbook, US EPA, 1996
[b/] Mean of male and female surface areas at midpoint of age range
[c/] Sample Calculation, Dermal Dose: (1000 mg male dose) x SA female/SA male = 871
[d/] Mean of male and female body weights 50th percentile; Exposure Factors Handbook, US EPA, 1996
[e/] Sample calculation: Potential Exposure (male) = Dermal Dose (1000 mg)/BW (78.1kg) = 12.8 mg/kg
[f/] Absorbed Daily Dosage = Dermal dose (mg/kg) x 8.4% (Selim, 1992; Selim *et al*., 1995)

Sanborn, WHS, 1999

When the ADDs in Tables 14 and 15 are compared, substantial differences exist for the youngest age group. The nearly 2-fold difference in ADDs for the child <12 y is related to the difference in the method of estimating the dermal dose. Both of these exposure scenarios (Tables 14,15) assume only one application per day. The differences between the estimated ADD values in Table 12 compared to 13, 14 or 15 relate to the absence of amortization of single applications over time.

In addition to the ADDs calculated in Table 15, seasonal average daily dosages (SADD) and annual average daily dosage estimates (AADD) may be required for comparison to some toxicology endpoints. Table 16 contains these estimates.

Table 16: DEET Absorbed Dosages - Daily, Seasonal and Yearly (µg/kg/day)

Value	Adult Male	Adult Female	Child 12-17	Child < 12
ADD[a/]	1076	1119	1177	1661
SADD[b/]	132	138	145	204
AADD[c/]	50.8	52.8	55.6	78.5

a/ Values from Table 15
b/ Seasonal Average Daily Dosage = ADD x 7.5 days/61 days, June, July.
c/ Annual Average Daily Dosage = ADD x 7.5 days/365/0.435 to account for use months other than of June/July

Sanborn, WHS, 1999

These data differ from those reported in Tables 12 and 13 because they were generated with a consideration that the dose applied reflects the surface area of the human. The most pronounced differences occur for the children <12. Using surface area to define the dose was the basis of Table 15. The SADD and AADD values in Table 16 were derived from the ADD values in Table 15.

Occupational Exposure

Exposure estimates are available for workers in mosquito control programs who used this repellent (Robbins and Cherniack, 1986). The data in Table 17, abstracted from this paper, also includes information from a US EPA document that estimated upper end exposures for the general population as well as workers in mosquito control programs in the Florida everglades. Everglade biologist exposures indicated below as mosquito control workers, have been included as a point of reference even though this level of use in California is not likely to occur because of the more temperate climate that results in lower populations of biting arthropods.

Table 17: Comparison of Occupational Exposures to DEET

		Dermal Exposure	
Group	Conc. %	Daily(g/day)	Seasonal (g)[a/]
Military Person	75	-	43
Mosquito Control	28.7	4.25	442
Mosquito Control (Upper 5%)	15-75	>2kg/7 mo	>1710

[a/] Use: May to October

Sanborn, WH&S, 1999, after Robbins and Cherniack, 1989

Clearly, the insect pressure present in the Florida Everglades occurs infrequently if at all in California. Nevertheless, it is important to be cognizant of the level of dermal exposure that may occur in other regions of the country. Using these dermal exposure values in Table 16 would result also in much higher ADDs as compared to those in Table 15. These data while informative for comparative purposes, do not possess the sample size and documentation to make them useful for the exposure assessment process for use of DEET in California.

EXPOSURE: INHALATION

The preceding estimates of exposure focused on the dermal route of exposure. The biological activity of DEET depends in part on its volatility, which is related to its relatively high vapor pressure (0.22 Pa). Evidence for evaporation after application may be found in a study that reported about 27% of a dose at 25 $\mu g/cm^2$ volatilized in 45 minutes after *in vitro* treatment of skin sections (Spencer *et al*., 1979). Estimates of exposure to DEET via the inhalation route cannot be based on active ingredient-specific data because none exist. Two types of inhalation exposures may occur, one short term (during application) and the other with a longer duration after application (evaporation from clothing/skin). The latter inhalation exposure component will be difficult to match with a toxicology endpoint because the amount volatilizing per unit time decreases resulting in a decreased exposure by inhalation. Further with respect to direct human inhalation exposure from aerosol products, DEET labels specifically state for these products that they should not be sprayed directly on the face or neck. Rather, the labels indicate that DEET should be sprayed first on the hands for subsequent application to other parts of the body (neck, ankles, *etc*.,).

For the estimation of inhalation exposure to products that contain DEET, consideration was given to the utilization of inhalation exposures (CFC propellant) from personal care products (hair spray, body spray, antiperspirant) as a surrogate (Hartop and Adams, 1989). These products, unlike DEET are directly sprayed either on the body or hair. Because these aerosol personal care products are directly sprayed on the skin or hair rather than as prescribed for DEET products, no estimates for inhalation exposure for this insect repellant have been derived using these data as a surrogate.

EXPOSURE APPRAISAL

The information used to estimate exposure of humans to DEET is substantial. There are data on dermal absorption in humans, metabolite characterization after controlled human exposure, human use data with respect to types of products, frequency of use, the site of application (skin or skin/clothing) and the amount applied for a single application. These data were derived from several surveys that have a relatively large sample size. The usage survey suggests that small children receive the same absolute dermal dose as an adult. Since this is not very reasonable because of the smaller surface area of small children as compared to an adult, an alternative exposure assessment based on surface area has been derived which should be used in the estimates of risk from DEET exposure.

From the data in Table 8, we can see that approximately 87-92% of the DEET used is formulated as products that can be sprayed on the clothing or skin. These contain label language that directs against applications to the face and neck. Thus, the relevance of the dermal penetration values determined in laboratory animals and humans could be questioned. In laboratory animal dermal absorption studies, DEET was applied with a pipette rather than by spray to ensure accurate dosing and acceptable material

balance. While direct application will result in more reaching the site of application, it may reduce the inhalation component of exposure. This is especially the case if devices are used to trap DEET evaporating from surface of the treated animals or humans. This would be of minor concern if biological monitoring were used to provide exposure information for dermal and/or inhalation routes. Given the relatively high vapor pressure of DEET, inhalation exposure is likely from both during spray application and evaporation from skin and clothing after application. However, because only small percentages of two metabolites were observed in the studies by Selim, 1992 and Selim *et al.,* 1995, it is not feasible at this time to determine whether biological monitoring can be used successfully to estimate exposure of DEET users. If the urinary metabolites, regardless of the percentage of applied dose, are found to be constant and linearly related to the excretion of radiolabel, and there is little intra- and/or interpersonal variation, then it may be possible to use biomonitoring to refine further exposure estimates.

There is no indication, from human or animal studies, that the dermal absorption or elimination after single or multiple doses will differ. For example, in laboratory studies in rats and monkeys, the rate of dermal penetration and subsequent elimination of DEET and its metabolites after multiple applications were similar to a single application (Moody *et al*., 1989). Therefore, when humans apply DEET several times in a day (which may occur where there is high arthropod pressure) the kinetics of penetration and elimination likely would not differ from those after a single dermal application.

Two issues have not been specifically addressed in this document, exposure via inhalation and upper-end exposure values for comparison to acute toxicology endpoints. Exposure to DEET via inhalation is likely to occur because most products sold are aerosol products that were reported from the use data to be sprayed on the clothing or the skin. Data to empirically base an inhalation exposure estimate do not exist. Therefore any estimate of exposure via inhalation would not be active ingredient-specific, empirically based and therefore not technically defensible. While other pesticides maybe sprayed from aerosol containers, the spray is directed **away** from the applicator and not **on** the user. Because data do not exist for estimation of inhalation exposure for products such as DEET that are sprayed on humans, an estimate for this route will not be derived even though it is unlikely to be zero. Earlier discussion indicated that personal care product exposure information was not appropriate for estimate of inhalation exposure. The best way to estimate exposure from products applied as sprays would be via biomonitoring which is not possible until more information exists about the usefulness of the urinary metabolite profile as a biomarker of DEET exposure.

With respect to high-end exposure estimates, the data in Table 11 can be used. Therefore, high-end exposure estimates from the dermal dose values can be estimated from the ratio of 95^{th} percentile to the mean. The ratio of the mean exposure to 95^{th} percentile is just slightly greater than 3. The high-end exposure estimate may be compared with acute toxicology data to estimate an acute risk while using DEET as an arthropod repellent.

The database for exposure to DEET contains sufficient exposure information to assess the risks associated with the use of this repellent. In particular, the number of human studies with DEET reduces the necessity of using animal data (such as dermal absorption) to derive an absorbed dosage for the assessment of risk.

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